PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference MXG/P33128	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/11650	International filing date *(day/month/year)* 20.10.2003	Priority date *(day/month/year)* 22.10.2002
International Patent Classification (IPC) or both national classification and IPC C07D209/26		
Applicant GLAXO GROUP LIMITED		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
05.05.2004	13.01.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Schuemacher, A Telephone No. +49 89 2399-7818

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/11650

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-39 as originally filed

Claims, Numbers

1-23 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 19,21,22

   because:

   ☒ the said international application, or the said claims Nos. 19,21,22 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-23
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-23
Industrial applicability (IA)	Yes:	Claims	1-18,20,23
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 19, 21 and 22 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Novelty, Article 33(2) PCT:

Reference is made to the following documents:

D1: WO 02 076925 A (ELI LILLY AND COMPANY, USA) 3 October 2002
D2: WO 02 24695 A (ORTHO MCNEIL PHARM INC) 28 March 2002
D3: WO 02 12190 A (ORTHO MCNEIL PHARM INC) 14 February 2002
D4: WO 00 06254 A (SOCIETE CIVILE BIOPROJET) 10 February 2000
D5: WO 01 23374 A (SMITHKLINE BEECHAM) 5 April 2001
D6: WO 01 066520 A (ONO PHARMACEUTICAL) 13 September 2001
-& EP 1 262 475 A 4 December 2002

In order to avoid any misunderstanding with regard to the content of D6, which is an International Patent Application in Japanese, its family-member patent EP 1262475 is used to assess novelty and inventive step of the present application.

With regard to the prior art disclosed in the documents cited above the subject-matter of the present application, i.e bicyclic benzamide compounds of formula (I) according to claim 1, appears to fulfil the requirements of novelty, cf. Article 33(2) PCT:

The compounds of D2-D4 differ from the claimed compounds on account of the nitrogen containing heterocyclic moiety, which never encompass isoindoline, indole, tetrahydroisoquinoline or tetrahydro-1H-3-benzazepine.

The generic disclosures in D5 and D6 overlap with present claim 1 but these documents do not contain specific examples of compounds which fall under the scope of present claim 1 (in D6, all the examples differ from the claimed compounds because they always have an acetic acid group on the indole ring and in D5, all the examples miss the phenoxy group). D5 and D6 are therefore not considered to anticipate the subject-matter of the present application.

The subject-matter of present claim 1 is totally included in the generic disclosure of compounds of D1 (see claim 1 of D1). Since there is no specific example in D1 that falls under present claim 1, the subject-matter of the present invention could be considered as a novel selection of the compounds of D1; the selection consists in choosing an isoindoline, indole, tetrahydroisoquinoline or tetrahydro-1H-3-benzazepine ring among the possible nitrogen-containing heterocycle formed by the groups R^7 and R^8 according to claim 1 of D1.
Thus, the requirements for novelty of Article 33(2) PCT are considered to be met.

2. Inventive step, Article 33(3) PCT:

The present application relates to bicyclic benzamide compounds as histamine H3-receptor ligands, which can be useful in the treatment of cognitive impairments in neurological diseases.
Document D1, directed to histamine H3-receptor modulators, is considered as the closest prior art document. As the present application can be regarded as a novel selection of D1, the technical problem underlying the present invention has to be seen in the provision of compounds with affinity for the histamine H3-receptor which have an unexpected advantageous effect in comparison with the compounds of D1.
Nevertheless, there is no evidence in the present application proving that the claimed compounds provide an unexpected surprising effect compared to the compounds of D1 and that this unexpected effect has its origin in the selection of an isoindoline, indole, tetrahydroisoquinoline or tetrahydro-1H-3-benzazepine ring among the possible nitrogen-containing heterocycle formed by the groups R^7 and R^8 according to claim 1 of D1.
In the absence of evidence of an unexpected effect provided by a representative set of compounds as claimed, Article 33(3) PCT cannot be considered to be satisfied.

3. industrial applicability:

For the assessment of the present claims 19, 21 and 22 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.